ORIGINAL ARTICLE

Cerebral function monitoring in neonates with perinatal asphyxia – preliminary results

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Abstract

INTRODUCTION: This study was based on foreign studies which confirmed the importance of amplitude- integrated electroencefalographic monitoring (aEEG) in the early prediction of the future neurological development of newborn infants with hypoxic syndrome. Our aim was to confirm the correlation between the type of aEEG trace and the level of brain damage in newborn infants in the early hours after the hypoxic event and to introduce this method into routine practice.
MATERIAL AND METHODS: With 56 newborn infants having suffered a perinatal hypoxic event (the average umbilical arterial pH was 6.95, the average BE value –17.3) and in 2 newborn infants after early postnatal hypoxia, aEEG monitoring was performed continually. The aEEG records of brain activity obtained were analyzed using the Hellström-Westas classification. The level of hypoxic-ischemic encephalopathy was evaluated according to the Sarnat-Sarnat classification. Assessment of future neurological development is not included in this work.
RESULTS: 12 (21%) of the 56 newborn infants did not develop any hypoxic-ischemic encephalopathy, 8 (14%) newborn infants had hypoxic-ischemic encephalopathy (HIE) grade I, 19 (35%) had HIE grade II and 17 (30%) had HIE grade III. The newborn infants without hypoxic-ischemic encephalopathy had normal or slightly abnormal aEEG trace. In the case of newborn infants who had HIE grade I, we recorded a normal or slightly abnormal aEEG trace. In the case of newborn infants who had HIE grade II, we recorded all types of aEEG trace – from normal to seriously pathological. Of the newborn infants who had HIE grade III, all had a pathological aEEG trace of "burst suppression patterns", low voltage pattern or flat trace pattern. The results show that if a newborn infant had a pathological type of aEEG trace in the early hours after a hypoxic event he or she later developed at least HIE grade II. 53% of the newborn infants with a flat aEEG trace later had HIE grade III.
CONCLUSION: Cerebral function monitoring is a non-invasive method used for the early assessment of the severity of a hypoxic event. As it could be used in the first few hours after birth, this method could be applied to select patients suitable for therapeutic hypothermia.

Abbreviations:
aEEG – amplitude integrated EEG
BE – base excess
BS – burst suppression
CFM – cerebral function monitor
CNV – continuous normal voltage
DNV – discontinuous normal voltage
FT – flat trace
HIE – hypoxic-ischemic encephalopathy
LV – low voltage
NICU – neonatal intensive care unit

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) as a result of a perinatal asphyctic event is still a serious problem in contemporary neonatology and the subsequent care treating newborn infants with serious neurological defects. In relation to the developing possibilities of neuroprotective therapy applied to newborn infants with early hypoxic syndrome, monitoring of brain activity is more often used to assess the prognosis of further development. At present the major interest in clinical studies is focused on hypothermia methods, either applied to the whole body or to the head only [1, 2, 3]. Experimental studies on animals have proved that the reduction in body temperature by 3 to 4 °C immediately after a hypoxic-ischemic event or after any other neurological damage protects the cerebral energetic metabolism, reduces cytotoxic oedema and histological damage and thus improves neurological development. Based on these results, it can be assumed that slight hypothermia could become a useful neuroprotective method in clinical treatment. Since the success of hypothermia is conditioned by its immediate application (within 12 hours or less), it is a question of whether we are able to quickly select patients suitable for hypothermia treatment [4]. The results from foreign studies have proved that aEEG monitoring performed soon after birth enables exact prediction of the neurological damage caused by hypoxia. This prediction could be made within 6 hours after the baby is born and thus could become a useful means of selecting patients suitable for hypothermia. The results of foreign studies show that the sensitivity of this method used to assess the development of a serious form of infant cerebral palsy reaches 83% and the specifics reach 90% [5, 6, 7].

This method is based on the continuous monitoring of basic brain activity using a cerebral function monitor (CFM). The output of this method is an aEEG trace [8, 9]. This method allows the long-term monitoring of changes in brain activity and could be applied at the patient's bedside immediately after he or she is hospitalised in the neonatal intensive care unit (NICU). A detailed description of this method was published in the NeoReviews journal [10].

AIM

1. To demonstrate the connection between the type of aEEG trace and the severity of subsequent hypoxic-ischemic encephalopathy and thus confirm the suitability of the method for the early prediction of future neurological development.
2. To introduce the method of the aEEG monitoring of hypoxic newborn infants into routine practice.

MATERIAL AND METHODS

In the period between April 2005 and September 2007 we monitored and subsequently assessed the continuous aEEG trace of 56 full-term newborn infants diagnosed with perinatal or early postnatal hypoxia. These newborn infants were hospitalized in the NICU at the Perinatal Centre of the Faculty hospital Hradec Králové and at the Perinatal Centre of České Budějovice Hospital, Inc. The average gestational age was 39 weeks (35–42), the average weight was 3129 g (1680g–3970g), the average umbilical arterial pH was 6.95 (6.51–7.32), the average base excess (BE) value was -17.3 (-26 – -1.0), the average Apgar score in the first minute was 2 (0–8), in the fifth minute 5 (0–9) and in the tenth minute 6 (0–10). The study included newborn infants with mild or serious hypoxia whose diagnosis was made based on the value of the umbilical pH, BE, Apgar score and/or on a failure of post-partum adaptation requiring immediate resuscitation in the delivery room. Two newborn infants suffered from a hypoxic event during the early postnatal period and needed immediate resuscitation and subsequent care at the NICU. The brain activity of all the children was monitored using a CFM 6000 instrument (Olympic Medical) with the help of hydrogel electrodes or disk electrodes. Monitoring began in the first hours after the newborn infants had been hospitalized in NICU; their average age was 6.65 hours (1.0–19). The first assessment of the prognosis based on an aEEG trace was made during the first 6–12 hours after birth. 4 newborn infants were connected to the CFM 6000 later, and thus the first prognosis was made at the age of 19 hours. The monitoring continued until the normal aEEG trace appeared, or at least for 72 hours. The average aEEG monitoring time was 52.8 hours (1.25 –192).

During the assessment the basic brain activity was analyzed according to the Hellström-Westas classification. The trace with the minimum amplitude of 7–10 uV and the maximum amplitude of 10–25 uV was regarded as continuous normal voltage (CNV). The trace with the minimum amplitude of under 5 uV and the maximum amplitude of over 10 uV was regarded as discontinuous normal voltage (DNV). The trace with the minimum amplitude of under 5 and the maximum amplitude of under 10 uV was regarded as pathological. The following types of aEEG trace – "burst-suppression" (BS), low voltage (LV) and flat trace (FT) are

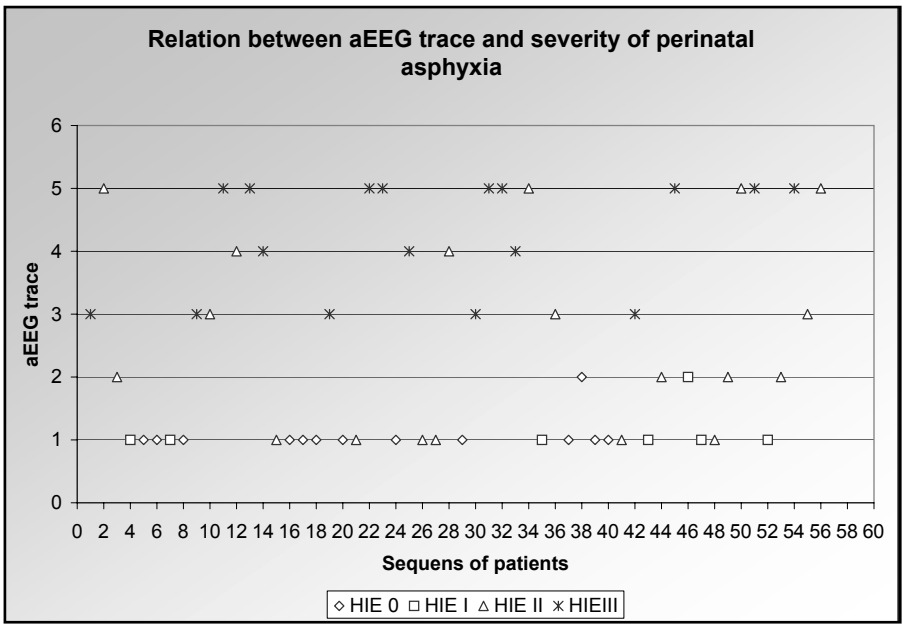

Figure 1: Relation between the aEEG trace and severity of perinatal asphyxia. Group of 56 newborn infants: 12 (21%) newborn infants without HIE, 8 (14%) newborn infants with HIE grade I, 19 (35%) newborn infants with HIE grade II, 17 (30%) newborn infants with HIE grade III

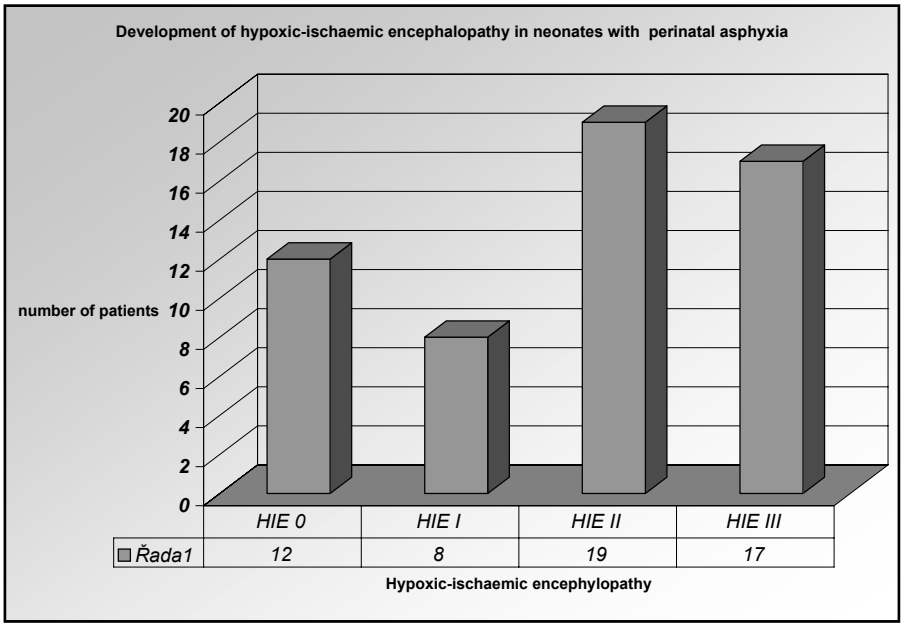

Figure 2: Relation between the aEEG trace and severity of perinatal asphyxia. Group of 56 newborn infants: 13 (23%) with a flat trace, 5 (11%) newborn infants with a low voltage trace (LV), 8 (13%) newborn infants with a "burst suppression" trace (BS), 6 (11%) newborn infants with a discontinuous normal trace (DNV), 24 (42%) newborn infants with a continuous normal trace (CNV)

considered pathological (see Figure 5) [10]. The degree of HIE was assessed using the Sarnat-Sarnat classification [11].

RESULTS

12 (21%) out of the 56 newborn infants did not develop any hypoxic-ischemic encephalopathy (HIE), 8 (14%) newborn infants had HIE grade I, 19 (35 %) had HIE grade II, 17 (30%) had HIE grade III (see Figure 1).

Of the 12 newborn infants who did not develop HIE, one (8 %) had a DNV trace with a fast modification to the CNV trace and 11 newborn infants (92 %) had a normal trace in which the cyclic changes were present, indicating an optimistic prognosis.

Of the 8 newborn infants who were diagnosed with HIE grade I, we identified a CNV trace in 7 newborn infants (87 %) and a DNV trace in the case of 1 newborn infant (13 %). Of the 19 newborn infants with HIE grade II, 6 newborn infants (31 %) had a normal aEEG trace, 4 newborn infants (21 %) had a DNV trace, 3 newborn infants (16 %) had an aEEG trace of "burst suppression" type (BS), 2 newborn infants (11 %) had a low voltage type of aEEG trace (LV) and 4 newborn infants (21 %) had a flat trace type (FT). 6 newborn infants with the normal aEEG amplitude trace were assessed as HIE grade II because they suffered from convulsions in the early postnatal period. 2 newborn

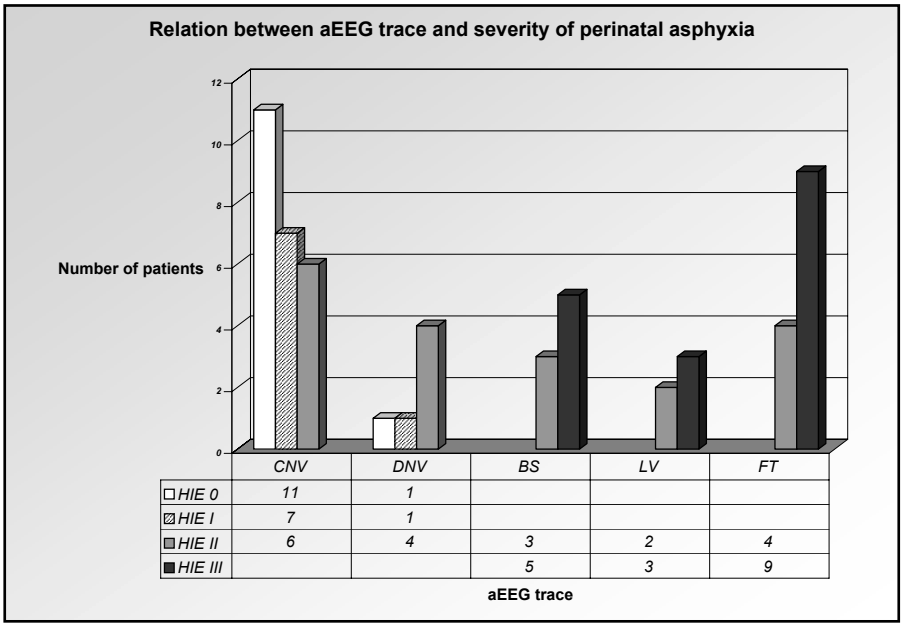

Figure 3: Development of hypoxic-ischemic encephalopathy in neonates with perinatal asphyxia: 12 newborn infants without HIE: 11(92%) with CNV, 1 (8%) with DNV; 8 newborn infants with HIE grade I: 7 (87%) with CNV, 1 (13%) with DNV; 19 newborn infants with HIE grade II: 6 (31%) with CNV, 4 (21%) with DNV, 3 (16%) with BS, 2 (11%) with LV, 4(21%) with FT; 17 newborn infants with HIE grade III: 5 (29%) with BS, 3 (18%) with LV, 9 (53%) with FT.
CNV- continuous normal trace
DNV- discontinuous normal trace
BS- "burst suppression" trace
LV- low voltage trace
FT- flat trace

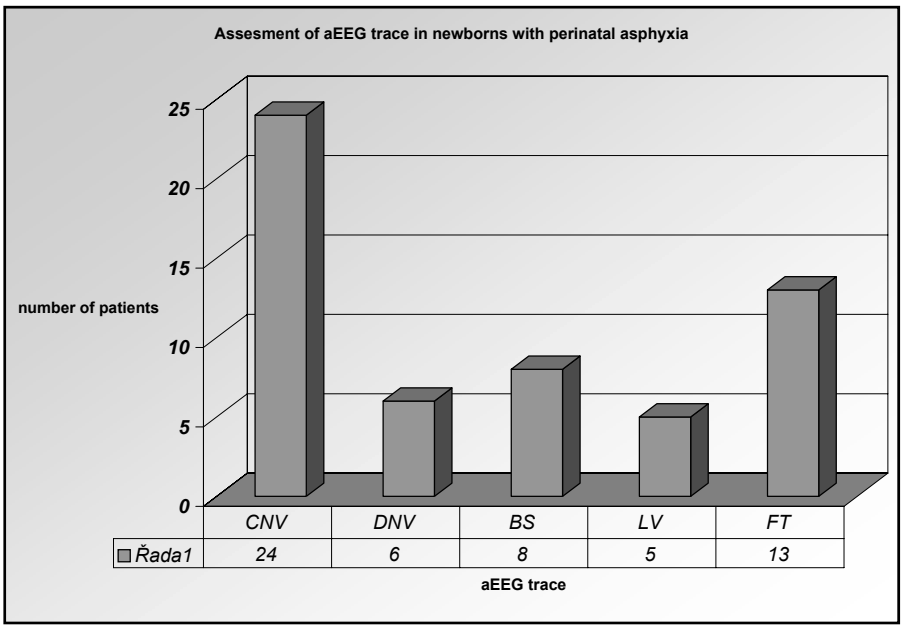

Figure 4: Assessment of the aEEG trace of newborn infants with perinatal asphyxia:
Axis x: patient no. in the waiting list
Axis y: type of aEEG trace (FT- flat trace, LV- low voltage trace, BS- "burst suppression" trace, DNV-discontinuous normal trace, CNV- continuous normal trace).

infants had suffered from clinical convulsions before the aEEG monitoring was started and the convulsions abated once Phenobarbital was applied; the rest of the neurological diagnosis was normal. 4 newborn infants had to be given an anticonvulsivant repeatedly and the paroxysmal activity was monitored on an aEEG trace. All the newborn infants with HIE grade III had a pathological type of aEEG trace, 5 newborn infants (29 %) had a "burst suppression" type of aEEG trace, in the case of 3 newborn infants (18 %) the trace was assessed as a low voltage type and in the case of 9 newborn infants (53 %) the trace was assessed as a flat type (see Figures 2, 3, 4).

From our results we can see that if a newborn infant had a pathological type of aEEG trace (BS, LV, FT) in the first hours after a hypoxic event, he or she later developed at least HIE grade II. 53 % of the newborn infants with a flat trace type later developed HIE grade III. Statistical data demonstrated the relation between the type of aEEG trace in the first hours after the hypoxic event and the degree of HIE to be at a significance level of 0.05. The probability of recording a pathological type of aEEG trace in newborn infants who developed HIE grade II –III (sensitivity) was 83 %. The specifics (the probability of recording a normal type of aEEG trace) in newborn infants without HIE or with HIE grade I were 90 %. The positive predictive value for the development of at least HIE grade II in the case of newborn infants with a pathological aEEG trace was 0.93; the negative predictive value (the probability that the newborn in-

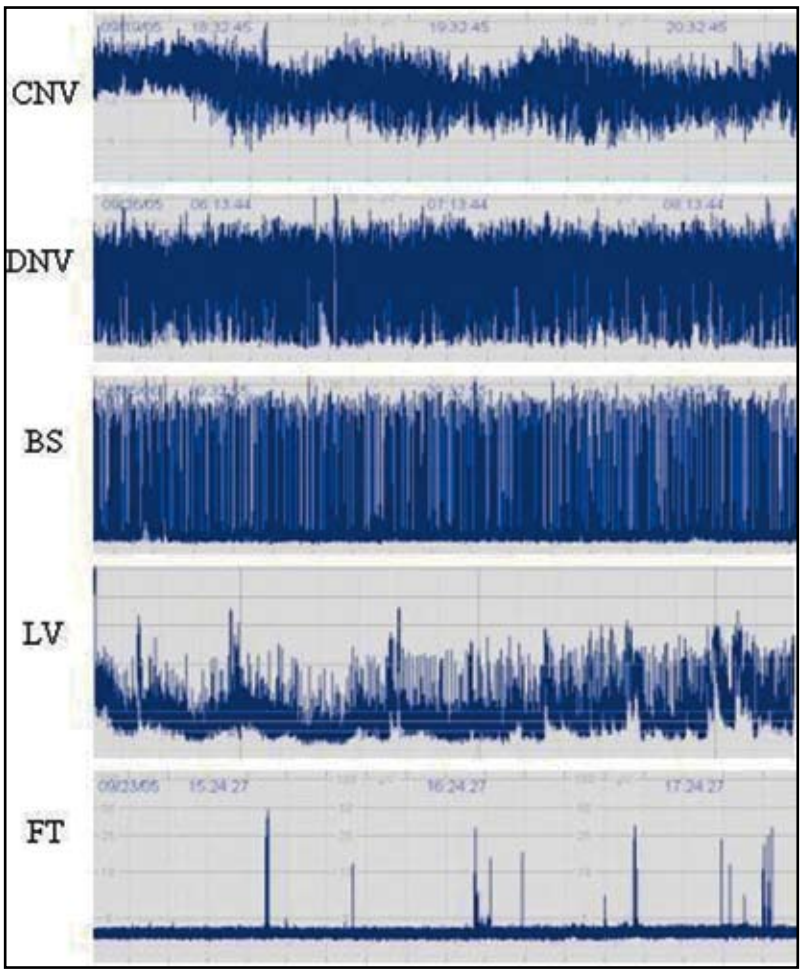

Figure 5. CNV – continuous normal aEEG trace with minimum amplitude 7–10 uV and maximum amplitude 10–25 uV; **DNV** – discontinuous normal trace with minimum amplitude under 5 uV and maximum amplitude over 10 uV; Pathological aEEG traces with minimum amplitude under 5 uV and maximum amplitude under 10 uV: **BS** – "burst suppression" trace; **LV** – low voltage trace; **FT** – flat trace

fants with a normal aEEG trace will develop a maximum of HIE grade I) was 0.75. The consensus coefficient (κ) for estimating the prognosis using the CFM method and the Sarnat-Sarnat classification was 0.66.

DISCUSSION

Our results, as with the foreign studies, show that when aEEG monitoring is applied it is possible to make a fairly accurate estimate of the severity of post-hypoxic brain damage shortly after the hypoxic event and before the full development of neurological post-hypoxic symptoms and thus assess the prognosis of the future neurological development at an early stage. In foreign studies, the relation between the aEEG trace and the neurological development of babies aged 12–24 months was assessed [5, 6, 7]. In our study we assessed the relation between the aEEG trace and the degree of HIE, which could be used as a means of further prognosis. In our study we also included newborn infants with moderate perinatal hypoxia who did not develop any HIE. Because of the low age of the newborn infants monitored, we could not monitor the neurological outcome to confirm the correlation between the type of aEEG trace and the subsequent neurological damage.

aEEG traces recorded in the hours after the birth correlate well with the degree of HIE and therefore this method could be appropriate for selecting suitable newborn infants for the early start of hypothermia treatment. As Azzopardi shows, hypothermia treatment should only be given to newborn infants who will probably suffer from a lesser degree of post-hypoxic brain damage after the application of hypothermia than they would suffer without it. It is not recommended to expose newborn infants with a good prognosis to the potentially toxic effects of this method. To get the best results hypothermia should be induced within 6 hours of the hypoxic event. The evaluation of future prognosis based on clinical symptoms might not be sufficient. On the other hand, the importance of aEEG monitoring recorded within 6 hours after the hypoxic event has

proved to be sufficient for determining the prognosis of the future development of newborn infants. Using aEEG monitoring we can select newborn infants at risk from the possible development of middle or serious encephalopathy for the hypothermia treatment. At the same time we can use aEEG monitoring to identify a group of newborn infants suffering from serious brain damage and whose neurological development would therefore be minimally influenced by the application of hypothermia treatment [4].

Gluckman et al. performed the first major multicentric study using selective hypothermia (head-cooling). Their study included newborn infants with moderate or serious brain damage or with convulsion activity recorded on the aEEG. Of those patients given hypothermia treatment, 55 % were seriously disabled or died. Of those infants that did not receive hypothermia treatment, 66 % were seriously disabled or died. When they removed from the hypothermic group newborn infants with a serious pathological aEEG trace in whose cases the minimal effect of hypothermic treatment could be expected, the result was 48 % of disabled newborn infants in the hypothermic group as opposed to 66 % in the normotermic group. The development of motoric damage was reduced from 28 % to 12 % of newborn infants [12]. Mrs. Shankaran et al. performed a multicentric study on 208 newborn infants who were given full-body hypothermia treatment. These infants were selected based on laboratory and clinical signs of medium-serious or serious hypoxia, without an aEEG recording. In the case of 205 infants the neurological development was monitored up to the age of 18 months. Death or medium-serious or serious retardation in the neurological outcome was monitored in the case of 44 % of the infants in the hypothermic group as opposed to 62 % in the normotermic group. [13]

According to the results of these studies, it seems that there is no significant difference as to whether hypothermia is indicated based on clinical and laboratory hypoxic signs, or based on the aEEG trace. However, none of these studies included evaluation of the neurological development of newborn infants who did not meet the criteria for inclusion in the studies (pH, Apgar score and neurological post-hypoxic signs soon after birth). On the other hand, from our group of newborn infants we, based on the laboratory signs of hypoxia used by Mrs. Shankaran et al. as a major criterion for selecting infants, would also include newborn infants with a normal aEEG trace in the hypothermic group.

The entire group of newborn infants was observed by Azzopardi et al., who used aEEG monitoring to select patients. Hypothermia treatment was started with 10 patients with a pathological aEEG trace (BS, LV, FT). After hypothermia treatment, 6 newborn infants had normal neurological development, 3 died and no information was available about 1 patient. 6 newborn infants had a normal aEEG trace, which is why they were not chosen for hypothermia, and none of them developed any serious HIE. The neurological development of these 6 newborn infants was normal at the age of 12 months. [4]

We assume that from the results published so far we cannot definitely decide whether selecting patients using an aEEG recording can significantly influence the effect of hypothermia or if it is only an ancillary method which could accelerate and simplify the selection of patients suitable for hypothermia. From the published studies it seems that patients with a moderate or serious pathological aEEG trace (DNV, BS, LV, FT), in whose cases we expect a reduction in serious post-hypoxic effects in their future neurological development, should be selected for hypothermia treatment [1, 3, 4, 12, 13, 14]. The results from other studies currently under way (TOBY-Great Britain, ICE-Australia, New Zealand and Canada) should extend our knowledge about the importance of hypothermia after a hypoxic event and of the use of aEEG monitoring to select patients.

A further indication for starting hypothermia treatment should be the recording of subclinical brain convulsions or clinical convulsions. According to the Hellström-Westas study, repeated convulsions (clinical or subclinical) were connected with the worse prognosis of patients, whereas the neurological development was normal in 50% of patients with only one brain convulsion episode [6].

In the case of newborn infants the diagnosis is complicated by the early occurrence of subclinical or clinical convulsions, especially in the case of newborn infants with HIE in whom the initial convulsions very often appear clinically, but the subsequent convulsion brain activity usually takes a subclinical course after the first dose of Phenobarbital [15, 16].

As the prognosis might be influenced by the indicated anticonvulsive therapy, it is better to record the aEEG continually, which can help to reveal subclinical convulsion brain activity without clinical correlative and enables us to monitor the effects of anticonvulsive therapy.

During the assessment of basic brain activity it is also necessary to consider the possible neurosedative effect of anticonvulsive therapy.

In some newborn infants with normal neurological development, after they had been given a dose of Phenobarbital, Ms Hellström-Westas observed inhibition of basic brain activity and recorded a "burst-suppression" type of aEEG trace. However, according to the clinical observation, more significant impact on brain activity can be monitored, especially in patients with more serious brain damage.

It is necessary to stress that the aEEG record has only one drawback. As Rennie says, even with continual monitoring we might not be able to record very short brain convulsions (less than 30 seconds) as well as focal convulsions and very low voltage convulsions [15].

In our group of patients, in the case of 22 newborn infants we recorded paroxysmal epileptic brain activity,

which was accompanied by clinical convulsions in the case of 11 newborn infants; 11 infants had only subclinical paroxysmal activity on their aEEG trace, without any clinical correlate.

CONCLUSION:

The aEEG is a simple non-invasive method used to monitor brain activity and predict future neurological development. In our work we have demonstrated the relation between the aEEG trace in the first few hours after birth and the degree of HIE, according to the Sarnat-Sarnat classification. This classification has been used for many years to assess the prognosis of future neurological development. The advantage of aEEG recording compared to the standard evaluation of the degree of HIE is that it enables earlier assessment of the patient's future neurological development (optimally in the first 6 hours of age), and therefore could become a useful means of selecting patients suitable for therapeutic hypothermia treatment. Recent foreign clinical studies have shown that in the case of well-selected newborn infants and when started early, hypothermia can contribute to a better prognosis of neurological development and therefore increase the quality of life of patients after perinatal hypoxia. Further studies must be carried out in order to be able to accurately indicate hypothermia treatment in clinical practice and to fully assess the contribution of EEG monitoring when selecting patients suitable for hypothermia treatment.

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